REMARKS

I. STATUS OF THE APPLICATION

Claims 1 – 20 were filed in the original application. In the Amendment and Response to the Restriction Requirement mailed September 11, 2006 claims 1–11 were cancelled, and claim 20 was amended. In the Amendment and Response to the Office Action mailed December 29, 2006, claims 12 and 16 were amended. In the present Amendment and Response to the Office Action mailed January 10, 2008 claims 12, 16 and 20 are amended, and claim 21 is added. The Applicants note that all amendments of claims are made without acquiescing to any of the Examiner's arguments or rejections, and solely for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),[1] and without waiving the right to prosecute the amended claims (or similar claims) in the future. Therefore, claims 1-21 are currently pending.

The Applicants submit that the amended and added claims provide no new subject matter. Support for the newly added amendments and claim may be found throughout the Specification at, for example, page 1, lines 10-13, page 2, lines 16-20, page 8, lines 2-4, and page 8, lines 15-17.

In the Office Action of January 10, 2008 the Examiner has made 1 objection and 4 rejections. The currently pending objection and rejections are:

1. The amendment filed 8/23/2004 is objected to under 35 U.S.C. 132(a) because it allegedly introduces new matter into the disclosure.
2. Claims 12 – 16 and 20 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement.
3. Claims 12 – 16 and 20 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement.

1 65 Fed. Reg. 54603 (Sept. 8, 2000).

4. Claim 20 is rejected under 35 U.S.C., 112 second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claims 12 – 16 and 20 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Zhang I (Zhang et al: Blood, vol 100, No.11, abstract 1; November 2002) (hereinafter "Zhang I").

II. STATUS OF THE OBJECTION

In the Office Action of January 10, 2008 the Examiner notes:

"The response asserts that table 1 present (sic) the nucleotide variants with respect to the wild type sequences and one of ordinary skill in the art would properly interpret table 1 in view of the wild type nucleotide and amino acid sequence. This response has been thoroughly reviewed but not found persuasive. The originally filed specification does not provide support for the sequences in table 1 as the specification does not teach that the sequences in table 1 are with respect to the wild type sequence. Furthermore the response did not address the amendment to the specification on page 6 with respect to SEQ ID No. 29-31, nor provide a detailed explanation regarding support for the originally filed disclosure for each new sequence."
(Office Action of January 10, 2008, page 4).

The Applicants respectfully submit that the rejection is defective for a number of reasons. First, the Examiner has failed to provide evidence that an ordinary artisan would not recognize that the variants presented in Table 1 are in reference to the wild type sequence. To the contrary, the Examiner's observations are unsupported by evidence, and therefore are conclusory and improperly made.

Second, the Applicants assert that an artisan of ordinary skill would clearly interpret Table 1 in view of the wild type nucleic acid and amino acid sequence, and that the Specification provides a detailed explanation regarding support in the originally filed

disclosure for each new sequence in Table 1. See, for example, the Specification at page 94:

> "We have deposited the correct full-length cDNA(~4.1 kb) sequence into GenBank (accession number AF537214). This gene, which we renamed *MCFD2*, spans 4 exons encompassing ~19 kb in the human genome and contains a 145 amino acid open reading frame, predicting a 16 kDa protein. Notable features of the amino acid sequence include a predicted signal peptide at the N-terminus and two calmodulin-like EF-hands for putative calcium binding at the C-terminus (Figure 2C).
>
> The full coding sequence and all intron/exon junctions of *MCFD2* were amplified by PCR from genomic DNA obtained from twelve F5F8D families. Seven distinct *MCFD2* mutations were identified, accounting for 9 of the 12 families (Table 1). Three of the 7 identified mutations result in frameshifts, including single nucleotide deletions in exon 2 (103delC) and exon 3 (249delT), and an 8 nucleotide deletion in exon 3 (263-270delTTGATGGC). Splice site mutations were identified in 4 families: a G to A substitution (309+1G->A) in the invariant GT of the intron 3 splice donor site (families 1 and 5), and a G to A substitution (149+5G->A) in the extended donor splice site consensus sequence of intron 2 (families 10 and 12). The remaining two mutations, found in families 4 and 9 respectively, result in single amino acid substitutions in the second putative EF-hand domain (D129E and I136T). These two missense mutations were excluded as common sequence polymorphisms by screening a panel of over 200 unaffected chromosomes." (Specification, page 94, lines 9-28.)

Third, the Preliminary Amendment presents the nucleotide variations of Table 1. in the context of their associated wild-type MCFD2 nucleic acid sequences. The Specification as originally filed includes the full -length MCFD2 DNA and amino acid wild-type sequences, together with Table 1. showing specific nucleotide variations, and their locations. Table 1. also includes Nucleic Acid and Amino Acid SEQ ID NOs that are each found in the Preliminary Amendment. Thus, the SEQ ID NOs in the preliminary

amendment each show full-length MCFD2 DNA sequences with the respective variations indicated in Table 1., and the consequent amino acid sequence of the corresponding Amino Acid SEQ ID NO. Because the ordinary artisan would properly interpret Table 1. in view of the wild-type nucleic acid and amino acid sequences disclosed in the originally filed Specification to arrive at the nucleic acid and amino acid sequences of the preliminary amendment, the preliminary amendment does add new matter *i.e.*, one skilled in the art would clearly recognize that the subject matter of the preliminary amendment is not "new matter". The Applicants observe that in the Office Action of January 10, 2008 the Examiner has failed to respond to, or even acknowledge, these facts.

Fourth, in the Preliminary Amendment filed 8/23/2004, SEQ ID NOs 29-31 of Figure 4B are clearly identified :

> "Figure 4B (SEQ ID NOS:29-31). The 5' untranslated region of the MCFD2 gene. Arrows indicate transcriptional start sites as determined by 5' RACE." (Preliminary Amendment of 8/23/2004, page 2.)

In turn, page 112 of the Sequence Listing clearly provides the sequences and SEQ ID NOs that are identical to the 3 sequences clearly shown in Figure 4B, and in the Preliminary Amendment of August 23, 2004. The Applicants submit that in the Office Actions of December 29, 2007 and January 10, 2008 the Examiner has never indicated what new matter the Examiner believes to be present in the Preliminary Amendment that is not present in the Specification, Drawings and Sequence Listing.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

III. STATUS OF THE REJECTIONS

A. Claims 12 – 16 and 20 Comply with the Enablement Requirement

1. In the Office Action of January 10, 2008 the Examiner argues

"In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches 7 mutations within the significantly large MCFD2 gene which are associated with F5F8D." (Office Action of January 10, 2008, page 10.)

And:

"Additionally, the amendment to the claims does not enable the specification. The recitation of a subject suspected of having a combined factor 5 and factor 8 deficiency does not enabled (sic) the claims." (Office Action of January 10, 2008, page 11.)

The Applicants respectfully submit that the Specification fully enables the claims. The Applicants observe that the Examiner has provided no evidence, law or reasoning for the Examiner's assertion regarding the amendment to claim 12 reading "providing a biological sample from a human subject suspected of having combined factor 5 and factor 8 deficiency". To the contrary, the Examiner's observations are unsupported by evidence, and therefore are conclusory and improperly made.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

2. In the Office Action of January 10, 2008 the Examiner argues:

"The specification does not teach a representative number of additional variants." (Office Action of January 10, 2008, page 11.)

The Applicants observe that the Examiner has provided no evidence, law or reasoning for the Examiner's assertion regarding what the Examiner believes to constitute "a representative number of additional variants." To the contrary, the Examiner's observations are unsupported by evidence, and therefore are conclusory and improperly made. The Applicants were the first to ever identify alleles of *MCFD2* that

cause bleeding disorders. As well, the Specification, Drawings, Claims and Sequence Listings of the present application disclose a wide range of examples of splice variants, single nucleotide deletions, multiple nucleotide deletions, frameshifts, truncations, and single nucleotide substitutions among other MCFD2 nucleotide and amino acid polymorphisms, with clear cut cause and effect relationships between variant MCFD2 nucleic acid and amino acid sequences and bleeding disorders. Because the specification provides a multiple predictable means for identifying multiple variants of MCFD2 which are correlated with F5F8 deficiency, the Applicants are entitled to the claimed genus.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

3. In the Office Action of January 10, 2008 the Examiner argues:

> "Additionally, the claim as amended encompass (sic) methods of detecting variants of MCFD2 in any subject, such as any animal, including dog, cat, mouse, rat, horse, etc." (Office Action of January 10, 2008, page 11.)
>
> And:
>
> "The response asserts that the claims are fully enabled and claim 12 has been amended to read "human" instead of "animal" (see page 7, last para. con't to page 8). It is noted that claim 12 has not been amended to read "human" instead of "animal" and as such the specification does not provide a predictably (sic) means for identifying additionally variants of the MCFD2 gene in any animal which are correlated with or indicated of F5F8D as is broadly encompassed by the claims." (Office Action of January 10, 2008 pages 11-12.)

The Applicants respectfully submit that the Specification fully enables the claims. However, in order to further the business interests of the Applicants, and while reserving the right to prosecute that original (or similar) claims in the future, the Applicants have amended claim 12 to read "a human subject". The Applicants assert that the amendment

adds no new matter and that support for the amendment may be found throughout the Specification.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

B. Claims 12 – 16 and 20 Comply with the Written Description Requirement

1. In the Office Action of January 10, 2008 the Examiner argues:

> "Furthermore claim 16 which recites a human embryo does not overcome the rejection as claim 16 only limits the embryo to human." (Office Action of January 10, 2008, page 16.)

The Applicants respectfully submit that the Specification provides ample written description of the claims. However, in order to further the business interests of the Applicants, and while reserving the right to prosecute that original (or similar) claims in the future, the Applicants have amended claim 16 to read "a human embryo, a human fetus, a human newborn, a human infant, a human child, and a human adult". The Applicants submit that the amendment adds no new matter and that support for the amendment may be found throughout the Specification.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

2. In the Office Action of January 10, 2008 the Examiner argues:

> "The recitation of "associated" appears to broadly encompass not only specific nucleic acid mutations which encode for amino acid changes the MCFD2 protein, but also to nucleotide variants which do not encode amino acid changes but may be found in the same sequence, for example, in a haplotype, with a particular nucleotide variant encoding a variant MCFD2 polypeptide. The specification has

been thoroughly reviewed but does not appear to provide support for the latter concept." (Office Action of January 10, 2008, page 16.)

The Applicants respectfully disagree with the Examiner's characterization of the Specification. However, in order to further the business interests of the Applicants, and while reserving the right to prosecute that original (or similar) claims in the future, the Applicants have amended claim 20 to read "detecting a variant MCFD2 nucleic acid sequence encoding said variant MCFD2 polypeptide."

In view of the above, the Applicants respectfully request that this objection be withdrawn.

3. In the Office Action of January 10, 2008 the Examiner argues:

"The specification does not teach or describe any nucleotide variants which do not result in a change in the amino acid sequence of MCFD2." (Office Action of January 10, 2008, page 16.)

The Applicants respectfully disagree with the Examiner's characterization of the Specification. However, in order to further the business interests of the Applicants, and while reserving the right to prosecute that original (or similar) claims in the future, the Applicants have amended claim 20 wherein the variant *MCFD2* nucleic acid sequence encodes a change in the amino acid sequence of the variant MCFD2 polypeptide, and added claim 21 wherein the variant *MCFD2* nucleic acid sequence prevents expression of normal MCFD2 polypeptide.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

C. Claim 20 is Definite

In the Office Action of January 10, 2008 the Examiner argues:

"Claim 20 is indefinite because it is unclear if the term is limited to nucleotide variations which are specifically encode (sic) an amino acid change or whether the term to encompass (sic) any variant in a nucleotide sequence which can also be found in a nucleotide sequence which encodes a variant polypeptide." (Office Action of January 10, 2008, page 18.)

The Applicants respectfully disagree with the Examiner's characterization of claim 20. However, in order to further the business interests of the Applicants, and while reserving the right to prosecute that original (or similar) claims in the future, the Applicants have amended claim 20 wherein the variant *MCFD2* nucleic acid sequence encodes a change in the amino acid sequence of the variant MCFD2 polypeptide.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

D. Claims 12 –1 6 and 20 are not Anticipated by Zhang

In the Office Action of January 10, 2008 the Examiner argues:

"It is noted that the rejection under 102(b) has been withdrawn and the rejection has been newly presented as a 102(a) rejection." (Office Action of January 10, 2008, page 19.)

The Applicants respectfully disagree with the Examiner's rejection. As specifically quoted by the Examiner, 35 U.S.C. 102 reads:

"A person shall be entitled to a patent unless-

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before invention thereof by the applicant for a patent." (Office Action of January 10, 2008, page 18.)

The Examiner expressly notes that Zhang I "is the applicant's own work" (Office Action of January 10, 2008, page 19). Because the invention was not known or used "by others", the Examiner's 35 U.S.C. 102(a) rejection is improper.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action dated January 10, 2008, have been addressed, and reconsideration of the application is respectfully requested. It is respectfully submitted that the Applicant's claims should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Dated: July 9, 2008

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